Treg to Th17 conversion in the dynamics of inflammation of the human skin.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Epidermal and dermal conditions
Study type	Observational invasive

Summary

ID

NL-OMON36028

Source
ToetsingOnline

Brief title
Treg to Th17 conversion in the human skin.

Condition

- Epidermal and dermal conditions

Synonym
psoriasis, rode schilferende huidziekte

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: psoriasis, rugulatory T cells (Treg), skin infkammation, Thelper-17 (Th17) cells

Outcome measures

Primary outcome

The main study endpoint will be the presence of IL-17 producing Tregs in the tissues obtained from healthy volunteers (after tape-stripping and LTB4 application) and patients with actinic keratosis treated with imiquimod 5%. Tissues will be analyzed using multicolour immunohistochemistry and immunofleorescence. We developed a sensitive triple staining that is based on the detection of CD4 and Foxp3 expression and IL-17 production. Co-localization of surface differentiation markers, transcription factors and cytokines will be verified by confocal-microscopy. Tissues will be visualized using microscopy, photographed and analysed using computer software (Image J).

Secondary outcome

We will use the mentioned in vivo models for human skin inflammation to analyze the balance of master transcription factors Foxp3 and RORγt through immunohistochemistry and immunofluorescence. We will study co-localization and expression of Foxp3, RORγt and IL-17 by confocal microscopy.

Study description

Background summary

Psoriasis is a chronic inflammatory skin disease and is caused by a deregulated immune system. In this project we will focus on different T-cell subsets contributing to the pathogenesis of psoriasis. More particularly, we will focus on regulatory T-cells (Tregs) and Thelper-17 cells (Th17). Tregs are important

in the *off-switch* of inflammation, and are characterised by the expression of CD25 and transcription factor Foxp3. Impaired functioning of these cells is considered in the context of several auto-immune diseases, such as psoriasis. In contrast, Th-17 cells are important in the *on-switch* of inflammation, and are characterised by the expression of transcription factor RORγt and the production of IL-17. Recent findings demonstrate that under pro-inflammatory conditions Tregs can differentiate in vitro into inflammation associated IL-17-producing cells. This conversion is also seen in the peripheral blood derived-Tregs from severe psoriasis patients. These cells may indeed be relevant to the local inflammatory processes in the human skin, as we saw IL-17-producing Foxp3-expressing CD4+ Tcells in lesional skin sections of psoriasis patients.

Study objective

With this project we would like to answer the following questions:
To what extent do we observe Treg toTh17 conversion in inflammation of the human skin, as elicited in response to general standardized skin injury (i.e. tape-stripping and topical LTB4 application)? And what can we learn from the application of imiquimod 5% (a TLR7/8 ligand and potent immune activator) on the human skin, concerning Treg and Th17 cells?

Study design

This study is an explorative observational study, in order to assess whether Treg into Th17 conversion is relevant to the *on switch* for inflammation of the human skin. We will demonstrate this by using in vivo models for inflammation, namely tape-stripping, LTB4 and imiquimod 5% application.

Study burden and risks

As twenty participants of our study are healthy volunteers, entering the study does not lead to direct benefit for them. Before the volunteers will give informed consent/assent, we will inform them that attending in this research is not in any way beneficial to the them. When the volunteer, despite of this, does wish to attend in this study, most likely he/she will do this to make a contribution to science. Considering this, we are of the opinion that participation in a study with short follow-up and only minimal invasive techniques, is legitimate. Tape stripping and LTB4 application has been carried out by us in the past and has been proven to be painless and without any discomfort. To obtain the biopsies, participants have to visit the hospital maximal 6 times. The punch biopsies are taken according to standard procedure and may be slightly tender. Scar formation does not occur or is barely visible. Conserning the patients with actinic keratosis, there will be no deviation from treatment procedures. Patients have to make two extra visits to obtain the biopsies. The extra visit to obatain the second biopsy can also serve as an

extra control after their treatment with imiquimod 5%. For some patients this might serve as a small benefit, that comes along with participating in this study, as normally the first control visit will be 2 months later. The punch biopsies are taken according to standard procedure and may be slightly tender. Scar formation does not occur or is barely visible.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy volunteers must meet the following criteria:
• Adults older than 18 years of age
• Volunteers must be willing to give a written informed consent
• Volunteers must be able to adhere to the visit schedule;Patients must meet the following criteria:

• Adults older than 18 years of age
• All patients have to have actinic keratosis
• The doctor and the patient decided that the best treatment option is field-treatment with imiquimod 5%
• Patients must be willing to give a written informed consent
• Patients must be able to adhere to the visit schedule

Exclusion criteria

Volunteers will be excluded from this study when any of the following criteria listed below are met:
• Children or adolescents younger than 18 years of age
• Volunteers with a history or signs of psoriasis
• Volunteers with a history or signs of other inflammatory skin diseases, for example atopic dermatitis
• Volunteers exposed to large amounts of sunlight or UV-radiation in the last week
• Volunteers using immunosuppressive agents like prednisone or methotrexate
• Volunteers with relevant co-morbidities
• Volunteers with a current condition involving an activated immune system, such as the flue or a recent vaccination;Patients will be excluded from this study when any of the following criteria listed below are met:
• Children or adolescents younger than 18 years of age
• Patients with a history or signs of psoriasis
• Patients with a history or signs of other inflammatory skin diseases, for example atopic dermatitis
• Patients exposed to large amounts of sunlight or UV-radiation in the last week
• Patients using immunosuppressive agents like prednisone or methotrexate
• Patients with relevant co-morbidities
• Patients with a current condition involving an activated immune system, such as the flue or a recent vaccination

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-10-2011
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	16-09-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL36165.091.11